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Diastereoselective Baylis–Hillman Reactions: The Design and Synthesis of a Novel Camphor-Based Chiral Auxiliary

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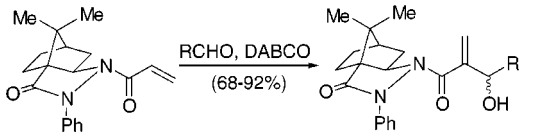
ABSTRACT



5

6a-e: α-OH (94-98% de)
7a-d: β-OH (94-98% de)

Reaction of chiral acryloylhydrazide 5 derived from novel auxiliary 4 with aldehydes in the presence of DABCO affords practical levels (up to 98% de) of β-hydroxy-α-methylene carbonyl derivatives, and high optical purity of both diastereomers of 6a–d and 7a–d can be obtained by changing the solvent.

The synthesis of both enantiomers of a chiral compound is a very important task in asymmetric synthesis. To attain this goal, traditional methods require the use of either antipode of chiral material to obtain stereoisomers with opposite configurations.[1] From a practical synthetic point of view, the preparation of both stereoisomers with excellent optical purity derived from the same chiral source is an attractive tool.[2] The Oppolzer camphor sultam is among the most promising chiral auxiliaries presently available in asymmetric reactions.[3] The search for structurally related auxiliaries for asymmetric synthesis continues, especially functional group modifications at the C10 position.[4] This fact and the great utility of the chiral sultam and related auxiliaries in stereoselective synthesis provided the motivation to develop a novel variant from which both diastereomers could be prepared using the same camphor scaffold. To the best of our knowledge, only a few examples of preparing both individual stereoisomers with high optical purity from a single enantiomer of chiral source have been reported.[2,4a,b]

The coupling of an α,β-unsaturated carbonyl/nitrile with an aldehyde (Baylis−Hillman reaction) provides useful

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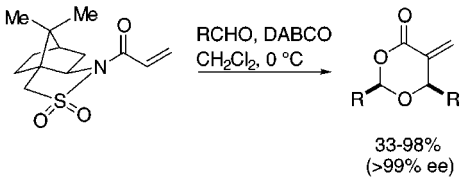
intermediates possessing a contiguous assembly of varied functionalities.[5] The reaction is mediated by a tertiary amine, and 1,4-diazabicyclo[2.2.2]octane (DABCO) is the most common catalyst employed. The resulting β-hydroxy-α-methylene carbonyl derivatives are versatile synthetic intermediates in organic synthesis.[6] The asymmetric version of the Baylis−Hillman reaction has attracted much attention in recent years.[7] Among these methods, the reaction of chiral Michael acceptors with an aldehyde is a conventional strategy.[8] Only a few examples, however, provide practical levels of β-hydroxy-α-methylene carbonyl derivatives. Leahy and co-workers have reported the use of camphor sultam in the Baylis−Hillman reaction.[8a] Excellent optical purity of lactones were obtained when camphor sultam was treated with various aldehydes in the presence of DABCO (eq 1).



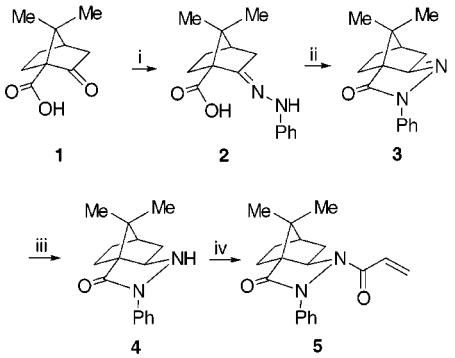
(eq 1)

It is noteworthy that the sultam auxiliary is automatically removed with the second equivalent of aldehyde.

In this Letter we wish to report the synthesis and use of **4** as a highly efficient chiral auxiliary for the asymmetric induction of the Baylis−Hillman reaction. Instead of providing the lactone products, high optical purities of β-hydroxy-α-methylene carbonyl derivatives can be obtained when **5** is treated with aldehyde. Further, either diastereomer of **6a**−**d** and **7a**−**d** can be prepared in high purity by the appropriate choice of reaction conditions.

Treatment of (+)-ketopinic acid[9] **1** with phenylhydrazine under acidic conditions provided **2** in 95% yield (Scheme 1). The cyclization proceeded smoothly when **2** was treated with $SOCl_2$ in EtOAc in the presence of Et_3N. The C−N double bond in **3** was reduced with $NaBH_4$ to give **4** as the sole product in excellent yield. Acylation of the auxiliary **4** with acryloyl chloride provided acryloylhydrazide **5** in 96% yield. The overall yield is 85% in four steps from the corresponding known starting material. The structure of **5** was unambiguously characterized by spectroscopic analyses and HRMS and further confirmed by single-crystal X-ray analysis.

Scheme 1



Reagents and conditions: i, Phenylhydrazine, acetic acid, CH_2Cl_2, 95%; ii, $SOCl_2$, Et_3N,EtOAc, 99%; iii, $NaBH_4$, MeOH, rt, 94%; iv, Acryloyl Chloride, Et_3N, CH_2Cl_2, 0 °C, 96%.

Treatment of compound **5** with DABCO (0.1 equiv) and acetaldehyde in neat conditions at room temperature for 8 h afforded the inseparable isomeric products **6a** and **7a** (75/25) in a total yield of 92% (Table 1, entry 1). The diastereomeric ratio was determined by HPLC analysis. An even more disappointingly low ratio of **6a**/**7a** (58/42) was observed when the reaction was carried out in THF at room temperature (entry 2). The diastereoselectivity was significantly improved when an aprotic solvent (DMSO) was used (entry 3). The reaction proceeded smoothly with a ratio of 97/3 in favor the formation of **6a**. The structure of **6a** was characterized by ^1H and ^{13}C NMR and HRMS analyses, and the absolute stereochemistry was established by single-crystal X-ray analysis. High diastereoselectivity was generally observed when different aldehydes were used (propionaldehyde, 3-phenylpropionaldehyde, 3-methylbutyraldehyde, and benzaldehyde) (entries 4−7). Interestingly, the sense of stereoselectivity was reversed when the reaction was carried out in a mixed solvent system. Thus, treatment of **5** with acetaldehyde in THF/H_2O (5/1) at room temperature for 96 h affords **6a**/**7a** in a ratio of 3/97 (entry 8). The influence of solvent polarity that causes the complete reversal of diastereoselectivity deserves special attention (compare entries 3, 8; 4, 9; 5, 10; and 6, 11). This creates a surprising scenario where apparently the transition state conformation is highly solvent-dependent. The reaction of **5** with benzaldehyde in THF/H_2O for 3 weeks resulted in a trace amount of products (entry 12). On the other hand, one of the unidentified product was isolated when α-branched aldehydes were used (entries 13 and 14). The structure was tentatively assigned to be a dimerized compound of **5** by ^1H NMR analysis.[10]

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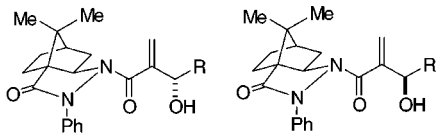
Table 1. Asymmetric Baylis−Hillman Reaction of Acryloylhydrazide **5** with Aldehydes[a]



6a R=Me
6b R=Et
6c R=CH_2CH_2Ph
6d R=CH_2CHMe_2
6e R=Ph

7a R=Me
7b R=Et
7c R=CH_2CH_2Ph
7d R=CH_2CHMe_2
7e R=Ph

entry	RCHO (R =)	solvent	time (days)	**6**/**7**	ratio[b]	yield (%)[c]	config[d]
1	Me	neat	1/3	**6a**/**7a**	75/25	92	*S*
2	Me	THF	1/2	**6a**/**7a**	58/42	82	*S*
3	Me	DMSO	2	**6a**/**7a**	97/3	88	*S*[e]
4	Et	DMSO	4	**6b**/**7b**	99/1	85	*S*[e]
5	$PhCH_2CH_2$	DMSO	4	**6c**/**7c**	99/1	80	*S*[e]
6	Me_2CHCH_2	DMSO	2	**6d**/**7d**	97/3	75	*S*[f]
7	Ph	DMSO	7	**6e**/**7e**	99/1	80	*S*[e]
8	Me	THF/H_2O	4	**6a**/**7a**	3/97	73	*R*
9	Et	THF/H_2O	3	**6b**/**7b**	1/99	85	*R*
10	$PhCH_2CH_2$	THF/H_2O	3	**6c**/**7c**	1/99	68	*R*
11	Me_2CHCH_2	THF/H_2O	3	**6d**/**7d**	1/99	81	*R*[e]
12	Ph	THF/H_2O	21	**6e**/**7e**		0	
13	^iPr[g]	DMSO	4				
14	^tBu[g]	DMSO	1/3				

[a] All reactions were carried out at 25 °C at atmospheric pressure. [b] Ratios determined by HPLC analysis on a J. T. Baker standard silica gel column (4.6 × 250 mm, 5 μm; hexane/^{i}PrOH = 95/5, 0.6 mL/min). Retention time: **6a** (30.4 min), **7a** (24.2 min); **6b** (20.5 min), **7b** (15.9 min); **6c** (17.4 min), **7c** (13.1 min); **6d** (15.2 min), **7d** (11.3 min); **6e** (14.8 min). [c] Yields of isolated products after flash column chromatography. [d] Major diastereomer of the newly generated stereogenic center. [e] The absolute stereochemistry was established by X-ray crystallography. [f] The absolute stereochemistry was established by analogy. [g] One of the unidentified products was isolated.[10]

The exact mechanistic explanation of this study remains unclear at the present time. The stabilization, however, of the zwitterion intermediate by intermolecular hydrogen bonding with the solvent molecules and/or the disruption of the intramolecular ionic bond by DMSO might play a crucial role in determining the stereochemical outcome. The avoidance of steric interaction between the R group of the aldehyde and the camphor skeleton might also be important. More information is needed before the puzzle can be answered. *In this study, either diastereomer of the β-hydroxy-α-methylene carbonyl derivatives with high optical purity can be obtained by the appropriate choice of reaction conditions*. It is noteworthy that both the degree of diastereoselectivity and the reaction rate appear to be concentration dependent.

In summary, an efficient route for the preparation of chiral auxiliary **4** has been developed, and compound **5** has been successfully used as a novel chiral Michael acceptor for the Baylis−Hillman reaction to achieve high stereoselection. Our procedure represents a simple and effective alternative for the highly diastereoselective synthesis of β-hydroxy-α-methylene carbonyl derivatives. *Moreover, both diastereomers of **6a**−**d** and **7a**−**d** with high optical purity can be prepared from the same chiral auxiliary by means of the proper choice of reaction conditions*. Further investigations on an enantiomeric version of the Baylis−Hillman reaction will be reported in due course.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **2**, **3**, **4**, **5**, **6a**−**e**, and **7a**−**d** and X-ray crystallographic data (table of atomic coordinates, hydrogen coordinates, and bond lengths and angles and ORTEP diagrams) for structures **5**, **6a**−**c**, and **6e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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